



11 Publication number: **0 659 413 A2**

12

# EUROPEAN PATENT APPLICATION

21 Application number: **94309470.6**

51 Int. Cl.<sup>6</sup>: **A61K 31/445, A61K 31/40**

22 Date of filing: **19.12.94**

30 Priority: **21.12.93 US 171388**

43 Date of publication of application:  
**28.06.95 Bulletin 95/26**

64 Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IE IT LI LU NL  
PT SE**

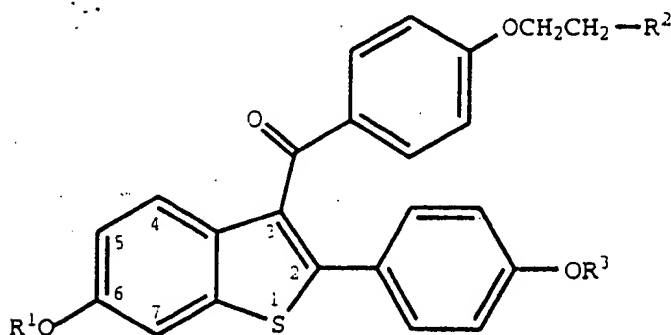
71 Applicant: **ELI LILLY AND COMPANY**  
Lilly Corporate Center  
Indianapolis Indiana 46285 (US)

72 Inventor: **Bryant, Henry Uhlman**  
7840 Camelback Drive  
Indianapolis, Indiana 46250 (US)  
Inventor: **Glasebrook, Andrew Lawrence**  
11410 Valley Meadow Drive  
Zionsville, Indiana 46077 (US)  
Inventor: **Grese, Timothy Alan**  
11407 Geist Valley Drive  
Indianapolis, Indiana 46236 (US)  
Inventor: **Phillips, David Lynn**  
9388 South County Road  
100 West Clayton, Indiana 46118 (US)

74 Representative: **Hudson, Christopher Mark**  
Lilly Industries Limited  
European Patent Operations  
Erl Wood Manor  
Windlesham Surrey GU20 6PH (GB)

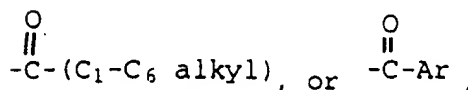
54 Inhibition of CNS problems in post-menopausal women.

57 A method of inhibiting one or more CNS disorders in a post-menopausal woman comprising administering to a female human in need of treatment an effective amount of a compound having the formula



(I)

wherein R<sup>1</sup> and R<sup>3</sup> are independently hydrogen, -CH<sub>3</sub>,



wherein Ar is optionally substituted phenyl;

R<sup>2</sup> is selected from the group consisting of pyrrolidine, hexamethyleamino, and piperidino; or a pharmaceutically acceptable salt or solvate thereof.

EP 0 659 413 A2



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



⑪ Publication number: **0 659 413 A2**

⑫

## EUROPEAN PATENT APPLICATION

⑪ Application number: **94309470.6**

⑤ Int. Cl.<sup>8</sup>: **A61K 31/445, A61K 31/40**

⑫ Date of filing: **19.12.94**

⑬ Priority: **21.12.93 US 171388**

⑭ Date of publication of application:  
**28.06.95 Bulletin 95/26**

⑮ Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE**

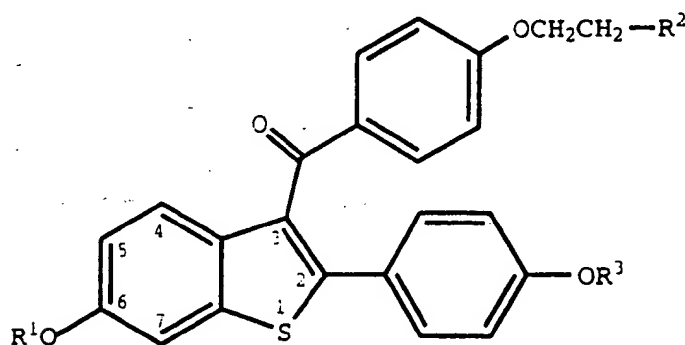
⑯ Applicant: **ELI LILLY AND COMPANY**  
**Lilly Corporate Center**  
**Indianapolis Indiana 46285 (US)**

⑰ Inventor: **Bryant, Henry Uhlman**  
**7840 Camelback Drive**  
**Indianapolis, Indiana 46250 (US)**  
Inventor: **Glasebrook, Andrew Lawrence**  
**11410 Valley Meadow Drive**  
**Zionsville, Indiana 46077 (US)**  
Inventor: **Grese, Timothy Alan**  
**11407 Geist Valley Drive**  
**Indianapolis, Indiana 46236 (US)**  
Inventor: **Phillips, David Lynn**  
**9388 South County Road**  
**100 West Clayton, Indiana 46118 (US)**

⑱ Representative: **Hudson, Christopher Mark**  
**Lilly Industries Limited**  
**European Patent Operations**  
**Erl Wood Manor**  
**Windlesham Surrey GU20 6PH (GB)**

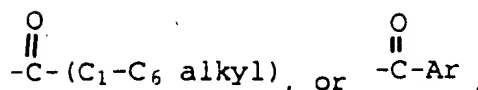
① Inhibition of CNS problems in post-menopausal women.

② A method of inhibiting one or more CNS disorders in a post-menopausal woman comprising administering to a female human in need of treatment an effective amount of a compound having the formula



(I)

wherein R<sup>1</sup> and R<sup>3</sup> are independently hydrogen, -CH<sub>3</sub>,



wherein Ar is optionally substituted phenyl;

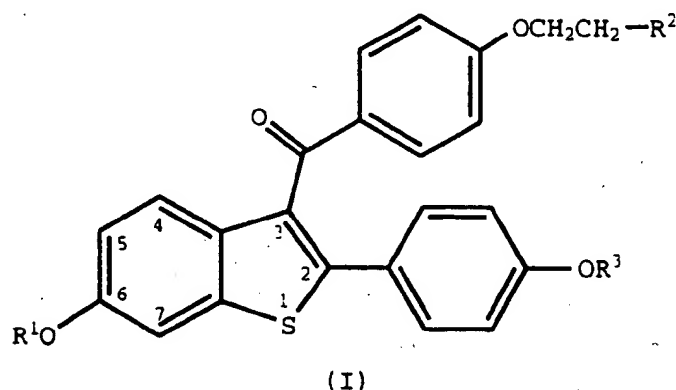
R<sup>2</sup> is selected from the group consisting of pyrrolidine, hexamethyleamino, and piperidino; or a pharmaceutically acceptable salt or solvate thereof.

In climacteric women, anxiety, depression, tension and irritability begin during the perimenopause and can be correlated to reduced estrogen levels and estrogen replacement therapy has been recommended for the treatment of these symptoms (Malleson J., *Lancet*, 2: 158, (1953); Wilson *et. al.*, *J. Am. Geriatric Soc.*, 11: 347 (1963)). The mechanism for protective effects of estrogen in this case is unknown, but may be related to potential effects of estrogen on biogenic amines such as serotonin (Aylward M., *Int. Res. Communications System Med. Sci.*, 1: 30 (1973)). To this regard circulating serotonin is reduced in post-menopausal women (Gonzales G., *et. al.*, *Maturitas* 17: 23-29 (1993)), and serotonin (as well as several other biogenic amines) have a putative role in behavioral depression.

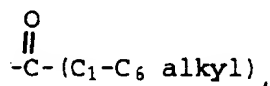
Phillips and Sherwin (*Psychoneuroendocrinology*, 17: 485-495 (1992)) reported that in surgically menopausal women given estrogen, scores in immediate and delayed recall tests are greater than in similar women not given estrogen. Two potential hypotheses might explain this effect. There is some evidence that partial estrogen agonists (or anti-estrogens) such as tamoxifen interact with the muscarinic receptor (Ben-Baruch G., *et. al.*, *Molec. Pharmacol.* 21: 287-293 (1982)), and muscarinic agonists ( $M_2$ ) are known to produce positive effects in a number of memory associated tasks and may have clinical relevance in Alzheimer's Disease. Another interesting possibility may be linked to neurokinins such as Substance P, which are known to have neurotrophic as well as memory-promoting effects (Thoenen H., *Trends in Neuroscience*, 14: 165-170 (1991); Huston J. *et. al.*, *Neurosci. Biobehav. Rev.* 13: 171-180 (1989)), thus, through an effect either at a neurotransmitter receptor in the CNS or at a neuropeptide receptor, a tissue selective estrogen agonist/antagonist could produce memory and cognitive enhancing effects. Such an activity would most relevantly be assessed in man, but a variety of animal models (i.e. maze learning, extinction etc.) are available for preclinical testing.

Perhaps the most frequent CNS related problem in climacteric women is the occurrence of hot flushes. While this undoubtedly is a somatic effect mediated by effects on the microvasculature, current evidence points strongly in the direction of CNS initiated effect (Lomax P., *et. al.*, *Pharmac. Ther.* 57: 347-358 (1993)). Therefore, a tissue selective estrogen agonist/antagonist like raloxifene might offer the ideal therapy providing the desired effect in the absence of untoward side effects on reproductive tissue.

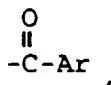
This invention provides methods for inhibiting CNS problems in a post-menopausal female comprising administering to a female human in need of treatment an effective amount of a compound of formula I.



wherein  $R^1$  and  $R^3$  are independently hydrogen,  $-CH_3$ ,



or,



wherein Ar is optionally substituted phenyl;

R<sup>2</sup> is selected from the group consisting of pyrrolidino, hexamethyleneimino, and piperidino; and pharmaceutically acceptable salts and solvates thereof.

The current invention concerns the discovery that a select group of 2-phenyl-3-arylbenzothiophenes (benzothiophenes), those of formula I, are useful for inhibiting CNS disorders in a post-menopausal woman. The methods of treatment provided by this invention are practiced by administering to a human in need of a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit one or more CNS disorders. The term inhibit is defined to include its generally accepted meaning which includes prophylactically treating a human subject to incurring the characteristics described, and holding in check and/or treating existing characteristics. As such, the present method includes both medical therapeutic and/or prophylactic treatment, as appropriate. CNS disorders are those disorders known to be included in the definition by those skilled in the art, which affect post-menopausal women, which includes anxiety, depression, mood swings, tension, irritability, motivational defects, memory loss and cognitive disorders.

Raloxifene, a compound of this invention wherein it is the hydrochloride salt of a compound of formula 1, R<sup>1</sup> and R<sup>3</sup> are hydrogen and R<sup>2</sup> is 1-piperidinyl, is a nuclear regulatory molecule. Raloxifene has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and pharmacology was that of an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, raloxifene does block the action of estrogen in some cells; however in other cell types, Raloxifene activates the same genes as estrogen does and displays the same pharmacology, e.g., inhibit bone loss, lower serum lipids. As a result, raloxifene has been referred to as an anti-estrogen with mixed agonist-antagonist properties. The unique profile which raloxifene displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the raloxifene-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although raloxifene and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not easily predicted and is unique to each. This is not to say, however, that the mechanism of action is necessarily mediated either at all or in part, through the estrogen receptor per se.

Generally, the compound is formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally, and may be formulated as sustained release dosage forms and the like.

The compounds used in the methods of the current invention can be made according to established procedures, such as those detailed in U.S. Patent Nos. 4,133,814, 4,418,068, and 4,380,635 all of which are incorporated by reference herein. In general, the process starts with a benzo[b]thiophene having a 6-hydroxyl group and a 2-(4-hydroxyphenyl) group. The starting compound is protected, acylated, and deprotected to form the formula I compounds. Examples of the preparation of such compounds are provided in the U.S. patents discussed above. Substituted phenyl includes phenyl substituted once or twice with C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl.

The compounds used in the methods of this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanolic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate,  $\beta$ -hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propionate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferred salt is the hydrochloride salt.

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10

days and can be isolated by filtration or the solvent can be stripped off by conventional means.

Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates, as well as aliphatic and primary, secondary and tertiary amines, aliphatic diamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, methylamine, diethylamine, ethylene diamine and cyclohexylamine.

The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

The particular dosage of a compound of formula I required to inhibit one or more CNS disorders in a post-menopausal female, according to this invention, will depend upon the severity of the condition, the route of administration, and related factors that will be decided by the attending physician. Generally, accepted and effective daily doses will be from about 0.1 to about 1000 mg/day, and more typically from about 50 to about 200 mg/day. Such dosages will be administered to a subject in need of treatment from once to about three times each day, or more often as needed to effectively treat the symptoms.

It is usually preferred to administer a compound of formula I in the form of an acid addition salt, as is customary in the administration of pharmaceuticals bearing a basic group, such as the piperidino ring. It is also advantageous to administer such a compound by the oral route to an aging human (e.g. a post-menopausal female). For such purposes the following oral dosage forms are available.

#### Formulations

In the formulations which follow, "Active ingredient" means a compound of formula I.

#### Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

The ingredients are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules.

Examples of specific capsule formulations of the raloxifene that have been made include those shown below:

**Formulation 2: Raloxifene capsule**

	Ingredient	Quantity (mg/capsule)
5	Raloxifene	1
	Starch, NF	112
	Starch flowable powder	225.3
10	Silicone fluid 350 centistokes	1.7

**Formulation 3: Raloxifene capsule**

	Ingredient	Quantity (mg/capsule)
15	Raloxifene	5
	Starch, NF	108
20	Starch flowable powder	225.3
	Silicone fluid 350 centistokes	1.7

**Formulation 4: Raloxifene capsule**

	Ingredient	Quantity (mg/capsule)
30	Raloxifene	10
	Starch, NF	103
	Starch flowable powder	225.3
35	Silicone fluid 350 centistokes	1.7

**Formulation 5: Raloxifene capsule**

	Ingredient	Quantity (mg/capsule)
40	Raloxifene	50
	Starch, NF	150
45	Starch flowable powder	397
	Silicone fluid 350 centistokes	3.0

The specific formulations above may be changed in compliance with the reasonable variations provided.  
 A tablet formulation is prepared using the ingredients below:

**Formulation 6: Tablets**

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Cellulose, microcrystalline	0 - 650
Silicon dioxide, fumed	0 - 650
Stearate acid	0 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.1 - 1000 mg of active ingredient are made up as follows:

**Formulation 7: Tablets**

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.1 - 1000 mg of medicament per 5 mL dose are made as follows:

**Formulation 8: Suspensions**

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

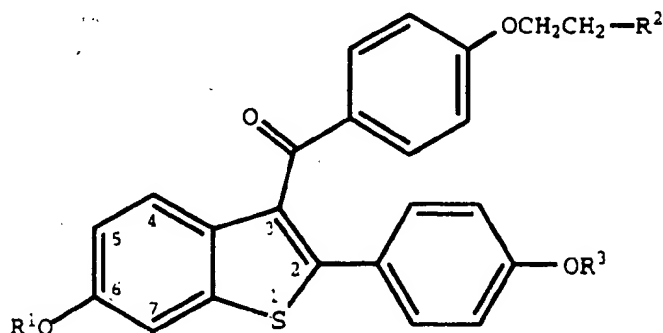
TEST PROCEDURE

Five to fifty women are selected for the clinical study. The women are post-menopausal, i.e., have ceased menstruating for between 6 and 12 months prior to the study's initiation, are in good general health, and suffer from one or more of the above-mentioned CNS disorders. Because of the idiosyncratic and subjective nature of these disorders, the study has a placebo control group, i.e., the women are divided into two groups, one of which receive the active agent of this invention and the other receive a placebo. Women in the test group receive between 50-200 mg of the drug per day by the oral route. They continue this therapy for 3-12 months. Accurate records are kept as to the number and severity of the above mentioned disorders in both groups and at the end of the study these results are compared. The results are compared both between members of each group and also the results for each patient are compared to the disorders reported by each patient before the study began.

Utility of the compounds of the invention is illustrated by the positive impact they have on one or more of the CNS symptoms/disorders when used in a study as above.

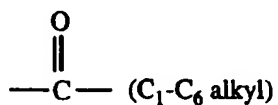
**Claims**

1. The use of a compound having the formula

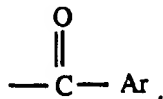


(I)

wherein R¹ and R³ are independently hydrogen, -CH₃,



or



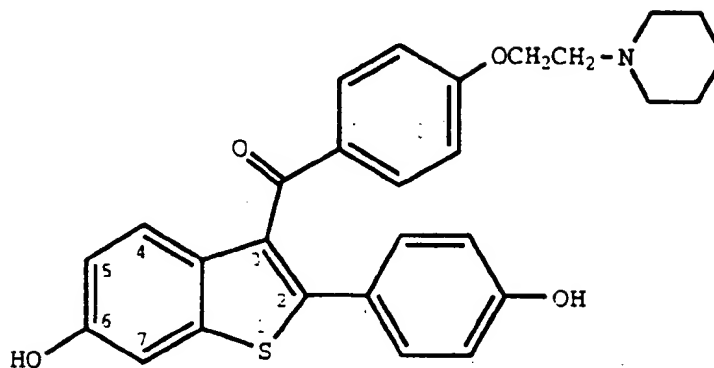
wherein Ar is optionally substituted phenyl;

R² is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting one or more CNS disorders in a post-menopausal female.

2. The use of Claim 1 wherein said compound is the hydrochloride salt thereof.



3. The use of Claim 1 wherein said medicament is prophylactic.
4. The use of Claim 1 wherein said compound is



or its hydrochloride salt.